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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,563	04/15/2004	Henriette Gourdeau	PHARMA 100 D2	6418

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EXAMINER

ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
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1614

MAIL DATE	DELIVERY MODE
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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/824,563	Applicant(s) GOURDEAU ET AL.	
	Examiner James D. Anderson	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-13, 15-26 and 34-37 is/are pending in the application.
- 4a) Of the above claim(s) 22 and 36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-13, 15-21, 23-26, 34, 35 and 37 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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CLAIMS 11-13, 15-26 AND 34-37 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed 3/2/2007 has been received and the appropriate papers, *i.e.*, those of 3/2/2007, have been entered into the application. Accordingly, claims 14, 27-33 and 38-50 are cancelled, claims 22 and 36 are withdrawn, and claims 11 and 15-18 are amended. In light of the amendments, as well as the remarks of Applicants at page 7 of their amendment, the rejections of the claims under 35 U.S.C. § 112, 1st Paragraph and the objection to the specification, as set forth in the previous Office action dated October 2, 2006 are hereby withdrawn.

Claims 11-13, 15-21, 23-26, 34-35 and 37 are presently under examination and are the subject of this Office Action.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

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Applicants' arguments have been considered but they fail to persuade the Examiner of error in his determination of obviousness. Firstly, Applicants argue that Chu *et al.* do not provide the motivation that would lead one skilled in the art to an embodiment in accordance with Applicants' claimed invention (page 8). Applicants argue that Chu *et al.* disclose a long list of possible cancers to be treated as well as a long list of additional chemotherapeutic agents that could be administered in combination with (-)-L-OddC. As such, Applicants assert that there is no reason why one of ordinary skill in the art would go beyond the list of agents disclosed in Chu *et al.* and combine another agent with (-)-L-OddC. This is not persuasive because the disclosure of Chu *et al.* sets forth a broad teaching that compounds such as (-)-L-OddC can be used in the treatment of cancer, both alone and in combination with other chemotherapeutic agents. The skilled artisan would recognize that the list of agents disclosed in Chu *et al.* is not all-inclusive, but is simply a representation of suitable agents. As such, the disclosure of Chu *et al.* is in no way limited to those agents specifically disclosed. In fact, Applicants acknowledge that chemotherapy in leukemia usually involves a combination of two or more anti-cancer drugs (page 2 of specification). Cytarabine is recognized by Applicants as a drug commonly used in combination with other therapeutic agents in the treatment of leukemia (*id.*). As such, no unobviousness is seen in combining cytarabine with (-)-L-OddC as disclosed in Chu *et al.*, because the skilled artisan, when presented with the broad disclosure of Chu *et al.*, would recognize that if one wants to treat leukemia, it would be beneficial to combine (-)-L-OddC with another agent commonly used in the treatment of leukemia. Applicants ask why one would select leukemia as the cancer to be treated (page 9 of Arguments). The simple answer is that Chu *et al.* explicitly recite leukemia as cancers that may be treated with (-)-L-OddC (page 6, lines

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22-28) and even provide *in vitro* results of such treatment (Table 2, page 35). Applicants also ask why one would select an agent such as an interleukin, from the long list of specific anti-tumor agents disclosed. This has been addressed *supra*. Simply put, Chu et al. specifically disclose interleukin as a drug that can be administered with (-)-L-OddC (page 8, line 6). The impetus to combine two (or more) agents to treat cancer is found throughout the prior art and acknowledged by Applicants. The simple fact is that combining two known anti-cancer agents to treat a cancer for which each is individually known to treat is obvious and routinely done in the prior art. The fact that the instantly claimed combination has not been previously applied to treat leukemia is the very reason this is a rejection of obvious, not anticipation.

Claims 11-13, 15-21, 23-26, 34-35 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chu *et al.* (WO 96/07413) (prior art of record) in view of Advani *et al.* (Blood, 1999, vol. 93, no. 3, February 1, pages 787-795) and Jamkubowski *et al.* (Leukemia, 1995, vol. 9, pages 1799-1804) (all of record).

The instant claims are drawn to a method of treating leukemia by administering a combination of cytarabine, (-)- β -L-dioxalane-cytadine (β -L-OddC) and an additional chemotherapeutic agent such as PSC 833.

Chu *et al.* disclose the use of (-)-(2*S*,4*S*)-L-(2-hydroxymethyl-1,3-dioxolan-4-yl)cytosine (also referred to as (-)-OddC, L-OddC, or (-)-L-OddC) in the treatment of cancer (page 5, lines 17-27; page 47, Claim 12). The compound is administered as its substantially “-“ enantiomer (*i.e.* free of the “+” enantiomer) (page 6, lines 6-11). Chu *et al.* define “enantiomerically enriched” to refer to a nucleoside composition that includes at least approximately 95%, and

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preferably approximately 97%, 98%, 99%, or 100% of a single enantiomer of that nucleoside. In a preferred embodiment, (-)-L-OddC or its derivative or salt is provided in a nucleoside composition that consists essentially of one enantiomer, *i.e.*, as the indicated enantiomer (the L-enantiomer) and substantially in the absence of its corresponding D-enantiomer (*i.e.*, in enantiomerically enriched, including enantiomerically pure form) (page 11, lines 6-18).

Leukemia is recited as one type of cancer (-)-L-OddC can be used to treat (page 6, lines 22-28).

It is further disclosed that (-)-L-OddC can be administered in combination with other anticancer agents, including interferons, interleukins and cytarabine (page 7, line 21 to page 8, line 20).

Figure 3 shows the results of treatment of P388 (an experimental lymphocytic leukemia cell line) leukemic mice with (-)-L-OddC. Further, the *in vitro* activity of (-)-L-OddC was demonstrated against several different leukemia cell lines (Table 2, page 35).¹ These tested leukemia cell lines correspond to an acute lymphoblastic cell line (CCRF-CEM), an acute promyelocytic leukemia cell line (HL-60), a chronic myelogenous leukemia (CML) cell line (K-562) and an acute lymphoblastic leukemia cell line (MOLT-4). Cytarabine is disclosed to be a useful agent in the treatment of acute myeloid leukemia and is also active against acute lymphocytic leukemia, and to a lesser extent, chronic myelocytic leukemia and non-Hodgkin's lymphoma (page 37, lines 23-33). The *in vitro* cytotoxic activity of cytarabine and (-)-L-OddC was compared against several cell lines, including an acute lymphoblastic cell line (CEM) (page 40). (-)-L-OddC was more potent than cytarabine against this leukemia cell line. Thus, Chu *et al.* disclose the treatment of cancer, including leukemias, with the instantly claimed compound. It is further

¹ It is noted that the leukemia cell lines in Table 2 are not properly identified. It is believed that RL-60(TB) is HL-60; BSOLT-4 is MOLT-4; and RPMI-2.26 is RPMI-82.26.

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disclosed that (-)-L-OddC can be administered with other agents, including the instantly claimed cytarabine, interferons and interleukins. (-)-L-OddC is provided in substantially the “-“ enantiomer and has demonstrated efficacy in the treatment of leukemia. Chu *et al.* further disclose that cytarabine is a known agent used in the treatment of different leukemias, including acute myeloid leukemia, acute lymphocytic leukemia, and to a lesser extent, chronic myelocytic leukemia. The reference does not disclose the administration of a combination of (-)-L-OddC and cytarabine further comprising PSC 833 or filgrastim in the treatment of leukemia.

However, Advani *et al.* disclose that a potential mechanism of chemotherapy resistance in acute myeloid leukemia (AML) is the multidrug resistance (*MDR-1*) gene product P-glycoprotein (P-gp). It is further disclosed that PSC 833 (PSC) has been used clinically in preliminary studies for treating poor-risk AML (page 787, left column). PSC, a potent inhibitor of P-gp, demonstrates low immunosuppression and renal toxicity (*id.*). The reference reports a phase II trial evaluating PSC in combination with mitoxantrone, etoposide and cytarabine in the treatment of AML patients with poor prognostic features.

Jamkubowski *et al.* disclose the treatment of patients with acute myelogenous leukemia with granulocyte colony-stimulating factor (filgrastim) (Abstract).

Given the above disclosures, it would have been *prima facie* obvious at the time the invention was made to combine (-)-L-OddC and cytarabine in a method to treat leukemia. The skilled artisan would have been motivated to do so given the disclosure of the WO reference which teaches the effectiveness of (-)-L-OddC in the treatment of leukemia cell lines and further suggests combining (-)-L-OddC with other agents to treat cancer. One skilled in the art would be further motivated to combine the two drugs in a single therapy given the known use of cytarabine

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in the treatment of leukemia. (-)-L-OddC and cytarabine are individually known in the art as agents for treating leukemia, whose efficacy when administered alone is well established for the treatment of a large number of different leukemias. It is generally obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980). The idea for combining said compositions flows logically from their having been individually taught in the prior art. *In re Crockett*, 126 U.S.P.Q. 186, 188 (CCPA 1960).

Accordingly, to establish obviousness in such fact situations it is not necessary that the motivation come explicitly from the reference itself (although the Examiner believes it does, as discussed *supra*). The natural presumption that two individually known anticancer agents would, when combined, provide a third composition also useful for treating cancer flows logically from each having been individually taught in the prior art. Applicant has presented no evidence (*e.g.* unexpected results) to rebut this natural presumption.

Accordingly, the claims are deemed properly rejected as being obvious over the applied references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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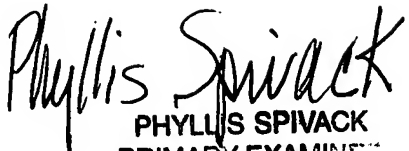
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James D. Anderson, Ph.D.
Patent Examiner
AU 1614

May 2, 2007



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PRIMARY EXAMINER